Immunodeficiency

Introduction

Primary immunodeficiency diseases are almost always **genetic**. They usually present **early in childhood**, and, if the child survives, will persist into adulthood. Primary immunodeficiency excludes secondary causes such as HIV/AIDS, diabetes, or systemic immunosuppression such as with high-dose glucocorticoids or other immunosuppressing or immune-modulating drugs. As you progress through this series of diseases, pay attention to **which cell** is compromised (B cell/antibody, complement, phagocytes, T cell) and at **what age** the disease presents.

Maternal IgG antibodies can easily cross the placenta to a growing fetus. Since mom has a robust immune system, she has lots of IgG against antigens. She inherently donates these IgG antibodies to the fetus, peaking in the third trimester. Babies expresses **neonatal tolerance—**an intentionally downregulated immune system—meaning that the baby has no immune system of its own. The lack of an immune system means that **premature infants** will be at higher risk of infection. The peak of maternal IgG antibody transfer to the fetus may not have occurred in a very premature infant. Because the half-life of IgG is about 30 days, the mother's IgG antibodies hang around in a baby born at term (so has had transfer of IgG from the mother in utero) for about six months. It is around this time (6 months old) that a baby is able to begin producing its own antibodies. So . . . if baby's going to have a problem with immunodeficiency, the real problems often don't start presenting until after month 6.

Antibody Deficiency (B Cells Broken)

X-linked agammaglobulinemia, or Bruton agammaglobulinemia. Either name is quite good. The inheritance pattern is X-linked recessive, so **boys** will be affected much more often than girls. This is because girls have two chances at a good copy. The defect is in a **tyrosine kinase** that prevents maturation of the B cell from the pro-B-cell to the pre-B-cell stage. Without this kinase, NO mature B cells can be made. Since NO mature B cells are ever made, no plasma cells are produced. This means that there's no surface IgM, no antigen presentation, no somatic hypermutation, no isotype switching—nothing. No immunoglobulins at all!

A-gamma-globulin-emia means no-gamma-globulins-in-the-blood. So there's a **complete deficiency of IgM, IgA, IgE, and IgG**. And keep in mind that because no mature B cells are released from the bone marrow, there are no B cells circulating in the peripheral blood in these patients. So if you were to check the blood of a patient with X-linked agammaglobulinemia, you would find NO B cells and NO immunoglobulins. None. How do these patients present clinically? Consider what is lacking and how that would contribute to risk of infection; Antibodies are particularly useful against **encapsulated bacteria**, so these patients often present with recurrent sinopulmonary infections (otitis media, sinusitis, bacterial pneumonia) with encapsulated organisms (most commonly *Streptococcus pneumoniae, Haemophilus influenzae* type B, *Streptococcus pyogenes*, and *Pseudomonas*. Because T cells, NK cells, and phagocytes are normal in number and function, viral and fungal infections are less likely.

X-linked hyper IgM syndrome. Caused by a deficiency in the **CD40 ligand** on the T cell. The CD40 ligand is an essential costimulatory signal from the $CD4^+$ T cell to the B cell (binds to CD40 on the B cell) to induce isotype switching and somatic hypermutation in the B cell. B cells produce IgM inherently. If **isotype switching is broken**, no IgG, IgA, or IgE can be made. This doesn't prevent antigen presentation, germinal center formation, or B-cell proliferation. However, because the CD40L is so important for isotype switching and somatic hypermutation, a not-so-specific IgM antibody is the only antibody that is circulating in the blood. IgM stays IgM. There's a **preponderance of IgM**, with **absent IgA, absent IgE, and absent IgG**. Because the IgMs can still do an okay job against invading pathogens, some patients may present at an older age than some other immunodeficiencies

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such as X-linked agammaglobulinemia (where there are NO immunoglobulins to help fight infection). However, it wouldn't be unusual to diagnose this after evaluating a "more infection-prone child" who can always be treated successfully with antibiotics (although a clue in these patients is that it often takes a longer time to treat, or several courses of antibiotics to clear the infection). Note that unlike X-linked agammaglobulinemia, where the defect is isolated to B cells (and therefore a humoral/antibody immunodeficiency), X-linked hyper IgM is due to a defect in CD40 ligand. This ligand is important for costimulation of $CD4^+$ T cells. Therefore not only might you see recurrent sinopulmonary bacterial infections but also infections common to those with T cell dysfunction such as PJP (*Pneumocystis jirovecii* pneumonia). This makes X-linked hyper IgM syndrome a **combined immunodeficiency**, meaning it affects both the T-cell- and B-cell-related branches of the immune system.

IgA deficiency is the most common immunodeficiency in the world. However, it is often **asymptomatic**, so most people don't even know they have it. IgA is the humoral defense mechanism used in mucosal surfaces like the GI and respiratory tracts. Those with IgA deficiency often have recurrent sinopulmonary infections (otitis media, sinusitis, bronchitis, pneumonia) and may have an increased susceptibility to GI viruses or to chronic diarrhea. By definition, all other antibody levels including **IgG levels are normal** in those with IgA deficiency. Although it **usually presents** in children, clinical presentation at any age is possible. Other than recurrent infections, a classic presentation of IgA deficiency is a Type 1 hypersensitivity reaction to a blood transfusion. The reason for the reaction is as follows. IgA occurs naturally in the blood of most people, so it will be in most transfused blood. Those with IgA deficiency lack IgA, so the body doesn't recognize IgA as a "self" protein. After a transfusion, the body therefore may produce antibodies against IgA, such as IgE anti-IgA (IgE that recognizes the Fc portion of the IgA antibody). The **next time** that person with IgA deficiency is given a blood transfusion the IgE that is specific to foreign IgA will recognize the donor's IgA. The IgE sits on a mast cell and waits for the antigen to bind to the Fab portion. Once it does, the IgE sends a signal to the mast cell to degranulate (release all of its contents such as histamine, tryptase, and others) which results in an anaphylactic reaction. In short, the foreign IgA causes a **massive antibody reaction** because of IgE that recognizes and binds to it.

Hyper IgE syndrome is caused by a **JAK-STAT mutation.** The mutation leads to impaired T_H17 function, shunting T-cell activation towards a T_H2 response, and results in increased IgE levels. The STAT mutation also reduces the function of $CD4^+$ and $CD8^+$ T cells, impairs B-cell differentiation and affects the development of bones and connective tissue. As a result, these patients have a particular clinical picture; Recurrent bacterial infections of the skin and lung, eczematous dermatitis, elevated IgE and skeletal (**retention of primary teeth**) and connective tissue abnormalities.

Complement

Complement is one of the immune system's ways of fighting bacterial infections, particularly encapsulated bacteria. Recall that the main way this occurs is through a complement cascade that results in the deposition of C3b on the bacteria (**opsonization**). Once opsonized, circulating phagocytes can easily recognize these labeled bacteria, phagocytose them, and present to/activate the adaptive immune system. C3a and C5a are released in the process of creating C3b, and help other immune cells reach the site of infection to help the phagocytes fight the invader. These C3a and C5a proteins do this through dilation of blood vessels (vasodilation) and calling immune cells to the site of infection (chemotaxis).

Because each of the complement proteins has its own role in the complement cascade, a deficiency of any single protein may have very different clinical consequences. Below we outline the major complement deficiencies and how missing those specific proteins creates a specific and sometimes distinct clinical picture. What each of these complement deficiencies has in common is that there is an increased risk of pyogenic infections with encapsulated bacteria. That clinical history in a patient should

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clue you in that there may be a complement deficiency, although other immunodeficiencies can result in infections with encapsulated bacteria as well. Therefore, a history of infection with encapsulated bacteria should make you think of complement deficiency, although it is not pathognomonic. Next, focus on the difference between each of the complement protein deficiencies that helps distinguish them from one another. This should help you to come up with a most likely specific complement deficiency that is causing the clinical picture for that particular patient.

C2 deficiency presents a little differently than many of the other complement protein deficiencies. If one is deficient C2, they are not only likely to present with recurrent pyogenic infections with encapsulated bacteria (as seen with the other complement deficiencies such as C3 deficiency) but they also have an increased risk of autoimmune disease, especially SLE (systemic lupus erythematosus). So, if you see a patient with an autoimmune picture AND recurrent pyogenic infections with encapsulated bacteria, think C2 deficiency.

C3 deficiency presents with severe pyogenic infections. This is because C3, as mentioned above, is an essential protein in the complement cascade in many ways. It not only helps with bacterial opsonization, but also as an anaphylatoxin, calling other cells to the site of infection. These patients often present with their first infections shortly after birth and continue to present with severe recalcitrant pyogenic infections. *Pneumococcus* > *H. influenzae* and *N. meningitidis*.

Deficiency in the **MAC attack complex** (C5b–9) causes **recurrent *Neisseria* species infections (meningococcal and gonococcal infections**). This requires vaccination against the organisms. So, if you see a clinical picture of *Neisseria* infections, think about deficiencies of the terminal complement system (C5b–9).

Remember, complement deficiencies in the **early classic cascade** means that the entire cascade is limited, resulting in more severe infections with a broad variety of encapsulated bacteria. The opsonization of C3b fails. The chemotactic abilities of C3a, C5a, and the MAC attack (C5b–9) must be activated through nonclassical mechanisms. Complement deficiencies in the **late cascade** (C5b–9) result in more specific infections with encapsulated bacteria (*Neisseria* species).

Phagocytosis

Leukocyte adhesion deficiency. Recall again how leukocytes get out of the bloodstream at the site of inflammation (#4: *Innate Immune Response*). Margination occurs from vasodilation—the cells make it to the sides of the vessel wall. In LAD, there's a deficiency in the **integrins** required for **emigration**—if the leukocytes can't hold onto the edge of the wall, they can't stop to get out. The infection is screaming for leukocytes, so the body makes more, trying to fill the demand, but no matter how many are made, none can get out of the capillaries and into tissue. So . . . there'll be a **high leukocyte-neutrophils count** (many being made and pumped into the circulation), but there will **be no pus** (cells can't get into tissue to cause pus). The classic clinical description and key feature is **delayed separation of the umbilical cord in a newborn** (which requires phagocytes to occur).

Chronic granulomatous disease. First, to understand this disorder we need to review how bacteria are lysed. Bacteriolysis occurs through the respiratory burst, through **aerobic** destruction of phagocytosed bacteria. The first step is the creation of an **oxygen-free radical** under the influence of **NADPH oxidase**. The second step is the formation of **hydrogen peroxide** via **superoxide dismutase**. For all catalase-negative organisms, hydrogen peroxide is fatal. For catalase-positive organisms, like staph, we need something stronger. Hydrogen peroxide is turned into **HOCl** (bleach) by **myeloperoxidase** (MPO). Which means . . . if MPO breaks, you can't kill staph. If NADPH oxidase fails, you can't kill anything.

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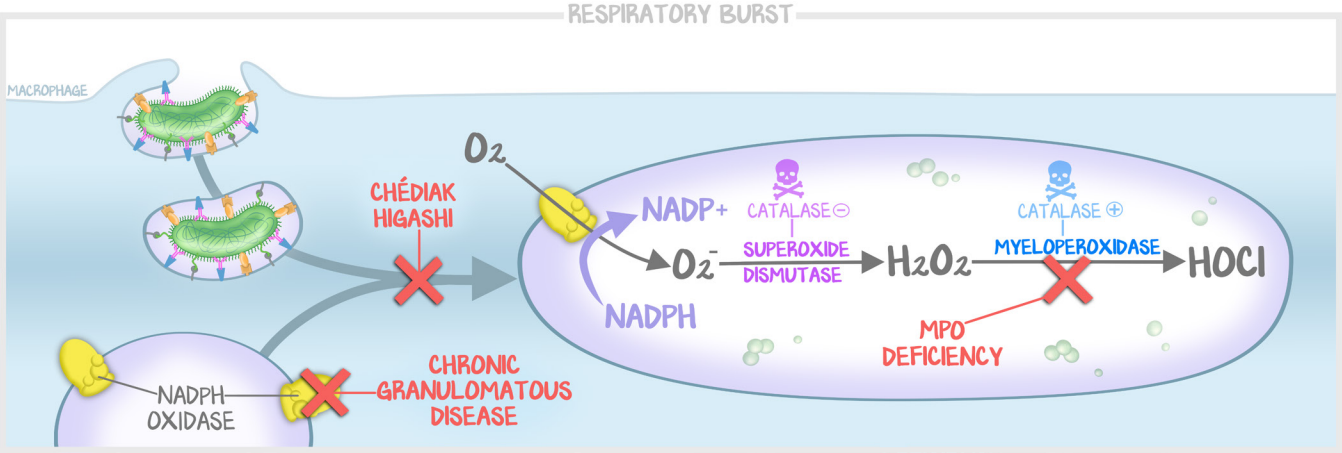

Figure 15.1: The Respiratory Burst
Phagocytosed bacteria within a phagosome are fused with a lysosome. Free oxygen radicals are generated and are used to form toxic compounds. NADPH oxidase makes the free radicals, superoxide dismutase makes hydrogen peroxide, and myeloperoxidase makes bleach. Hydrogen peroxide can kill catalase-negative organisms, and bleach is required to kill catalase-positive ones.

Chronic granulomatous disease is caused by an **X-linked recessive** mutation that causes the absence of **NADPH oxidase**; there's no respiratory burst. Without a respiratory burst, there's no formation of hydrogen peroxide and no formation of bleach. Which means that no bacterial infections can be contended against. Defense against all bacteria inside lysosomes begins with the respiratory burst. The **respiratory burst** can be assessed by two tests—the **nitroblue tetrazolium test** (a change to blue means intact, no color change means broken), and the chemiluminescence with dihydrorhodamine (glowing means normal, no glow means broken).

Myeloperoxidase deficiency limits the final step. Catalase-positive organisms (staph) can't be contended against, but catalase-negative organisms, like strep, can be killed.

Chédiak-Higashi is an **autosomal recessive** disorder that has to do with microtubule transport of lysosomes. Its other common name, **oculocutaneous albinism**, only describes one of its clinical features; but, as you will see, all of the clinical features have a connection to the defect in lysosomal transport.

T-Cell Deficiencies

T-cell immunity is often associated with fungi and viruses (whereas **B-cell immunity** is antibody-mediated against bacteria which then get phagocytosed). Keep this association in mind as we review the following defects that involve T-cell immunity.

DiGeorge syndrome, immunologically speaking, is strictly a deficiency of T cells. A chromosomal deletion at **22q11.2** causes a failure of the third and **fourth pharyngeal pouches** to develop properly, which leads to **thymic aplasia**. No thymus = no T cells. All of the problems have to do with failure of the third and fourth pharyngeal pouches to develop properly, so keep that in mind as you try to remember each of the common presenting findings in the syndrome. Patients characteristically have low-set ears, wide-spaced eyes, and an **absent thymic shadow** on chest x-ray. The lack of thymic development means T cells do not have a "school" to go to and they do not develop. Clinically, patients present with increased susceptibility to fungal and viral infections, as this is what T cells help protect against the most. Because T cells help B cells develop into plasma cells that produce antibody, DiGeorge patients may also present with antibody deficiency. They therefore may also have recurrent

sinopulmonary infections. Thymic transplant reverses the immunodeficiency, but not the physical features of the disease, as the latter are developmental. The mnemonic for DiGeorge syndrome is CATCH-22: Cardiac, Abnormal face, Thymic aplasia, Cleft palate, Hypocalcemia, and chromosome 22.

Wiskott-Aldrich Syndrome is an eponym for a deficiency of the WAS gene which encodes the **WAS** protein. The protein plays a critical role in actin cytoskeleton rearrangement. Wiskott-Aldrich is inherited in an X-linked recessive manner. The classic presenting clinical findings include **eczema** (usually in the first month of life), **thrombocytopenia** (results in petechiae, bruising and bleeding disorders), and **immunodeficiency** involving WBCs. Both B cells and T cells are affected, which results in the loss of both antibody and cellular responses, respectively. If immunoglobulins are checked, IgM and sometimes IgG will be low, meaning they are lacking the most important antibodies for fighting infection, especially early infection. This means that patients with WAS may present with any combination of infections, including bacterial (B-cell/antibody) infections and viral or fungal (T-cell) infections.

Severe Combined Immunodeficiency (SCID). Losing all your B cells (X-linked agammaglobulinemia) means no antibodies. But losing all your T cells means loss of the T_H1, T_H2, and T_H17 responses. Because T cells are essential for activating B cells to become antibody-secreting plasma cells and memory cells, losing T cells means there's also loss of B-cell function and antibody production. Without T cells, B cells receive no costimulatory signal to survive, and become anergic. Hence the reason why SCID is called a "combined" immunodeficiency. In addition, APCs have nothing to present to, so there are no cytokines. Effectively, there is **no immune system**, hence the term "severe". What will the labs show? You will see that there's a **greatly reduced number of lymphocytes on CBC**, and **flow cytometry** will show a paucity of T-cell markers (CD3, CD4, CD8). This is what the famous "bubble boy" had. Because mom's antibodies don't have much effect when there is no immune system to work with the antibodies, a baby with SCID will present much earlier in life (around **2 months)** than an isolated antibody deficiency patient such as XLA. Any exposure to any pathogen can be fatal; bone marrow transplantation is the only hope for these patients.

SCID (Severe Combined Immunodeficiency) is the description of immunodeficiency that affects both humoral (B cell) and cellular (T cell, NK cell) branches of the immune system. The name says it all; *severe* and *combined* are important key words to remembering this disease. All SCID affects T-cell development but only some cases of SCID directly affect B cell development. Note, however, that B-cell function depends on normal T cells. Therefore, the humoral immune system can be affected by a fault in T cells, even if there are normal numbers and function of B cells. SCID patients are often born looking normal and healthy. Their immune system has not had to work yet, as it has been covered in utero by the maternal immune system. However, they have early and severe life-threatening infections with bacteria, fungi, and viruses that a normal immune system can easily fight off. If not treated with a stem cell transplant, gene therapy, or enzyme therapy, they will not live beyond the first year or so of life.

SCID happens by three major mechanisms, although there are several others that are beyond the scope of this review. At this point, just focus on those that are here. Pay attention to the underlying gene defect and the inheritance pattern.

SCID due to adenosine deaminase deficiency. Adenosine deaminase (ADA) is a means by which purine metabolism is carried out. Other cells have alternative methods of processing purines. When ADA is absent, dATP (a toxic metabolite) accumulates, DNA replication is inhibited, and mitosis is halted. Cell lines that depend on development and proliferation (B cells, NK cells, and T cells) are affected. Those with ADA deficiency acquire it through an **autosomal recessive** inheritance pattern.

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SCID due to defects in RAG1 or RAG2 genes. RAG1 and RAG2 are essential for cleavage during VDJ recombination in T cells and B cells. Lack of these genes results in absence of T cells and B cells, as well as antibodies. Therefore, much like ADA deficiency, patients will have severe immunodeficiency affecting both cellular and humoral branches of the immune system. Also like ADA deficiency, RAG1 defects are **autosomal recessive**. NK cells do not depend on VDJ recombination, so NK cell numbers and function are normal in these patients.

SCID due to defective IL-7 receptor. This disorder has an **X-linked recessive** inheritance pattern. Because there's a **complete absence of** the interleukin-receptor of T cells, (the one that receives the IL-7 signal) there can be **no maturation of T cells**. Even if there were any mature T cells, there could be **no autocrine signaling** to prevent apoptosis. This is a defect ONLY of T-cell maturation and survival. However, without T cells there is no B-cell activation. Without B-cell activation there is no adaptive immune system, including antibody production.

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